

Have we overestimated the benefit of human(ized) antibodies?

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The infusion of animal-derived antibodies has been known for some time to trigger the generation of antibodies directed at the foreign protein as well as adverse events including cytokine release syndrome. These immunological phenomena drove the development of humanized and fully human monoclonal antibodies. The ability to generate human(ized) antibodies has been both a blessing and a curse. While incremental gains in the clinical efficacy and safety for some agents have been realized, a positive effect has not been observed for all human(ized) antibodies. Many human(ized) antibodies trigger the development of anti-drug antibody responses and infusion reactions. The current belief that antibodies need to be human(ized) to have enhanced therapeutic utility may slow the development of novel animal-derived monoclonal antibody therapeutics for use in clinical indications. In the case of murine antibodies, greater than 20% induce tolerable/negligible immunogenicity, suggesting that in these cases humanization may not offer significant gains in therapeutic utility. Furthermore, humanization of some murine antibodies may reduce their clinical effectiveness. The available data suggest that the utility of human(ized) antibodies needs to be evaluated on a case-by-case basis, taking a cost-benefit approach, taking both biochemical characteristics and the targeted therapeutic indication into account.

Introduction

The ability of antibodies to bind with precision to particular biological targets

has been harnessed over the last 30 years, resulting in significantly enhanced therapeutic options for patients in numerous disease indications. Originally, all therapeutic antibodies were polyclonal, but discovery of hybridoma technology allowed large volumes of antibodies with a single specificity to be produced. This technology was largely limited to production of murine-derived (usually mouse or rat) antibodies; as such, 80% of all monoclonal antibodies (mAbs) in clinical development in the 1980s were of murine origin.¹ Murine-derived antibodies, however, have historically been associated with undesirable properties including short serum half-life and the ability to trigger human anti-mouse antibody (HAMA) or human anti-rat antibody (HARA) development.^{2,3} Initial advances in the understanding of antibody structure and molecular biology have allowed some murine antibodies to be engineered as chimeric or humanized forms, which resulted in a reduction in these issues for some antibodies.^{2,3} Further improvements in antibody development technology resulted in phage display libraries and transgenic animals that allowed generation of human antibodies without the need for murine antibodies as starting material.

Human(ized) antibodies are generally viewed as safer alternatives to murine antibodies and are often developed instead of their murine counterpart, should one exist. This trend is evidenced by the small proportion of murine-derived antibodies in development or approved. Analysis of antibody development trends described by Reichert¹ suggests that, although 80% of all mAbs in clinical development during the 1980s were of mouse

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origin, this number dropped to 7% during the 2000s.¹ To further address the safety of human(ized) antibodies, we reviewed publically-available data for 38 human(ized) and 43 rodent-derived antibodies that have been tested in humans (Table 1). While there are certainly caveats when comparing antibodies that have been utilized in contrasting indications, particularly with patients in some cases undergoing different background therapies, the collected data suggest that human(ized) and rodent-derived antibodies triggered similar levels of acute phase and infusion reactions. While rodent-derived antibodies appeared to trigger anti-drug-antibody production at higher frequency, this phenomenon was usually negligible, resulting in little to no effect on overall clinical objectives. Interestingly, in some cases increased anti-drug-antibody production resulted in enhanced therapeutic outcome.

The data show that the assumption that safety gains will be made through human(ization) may be somewhat oversimplified. Reductions in acute phase reactions or anti-drug-antibody production have not been consistently observed. Attempts to reduce the pharmacological activity of certain agents through humanization, such as mitogenic abilities of antibodies targeting T cells, have resulted in only modest safety gains. A recent study highlighted the ability of humanized antibodies to stimulate CD4⁺ T cells through epitopes located within antibody complementarity determining regions (CDRs).⁴ On the other hand, events such as cytokine release syndrome (CRS) and anti-drug-antibody development may even play critical roles in the mechanism of action of certain monoclonal antibodies.⁵ Taken together, these findings suggest that interactions between an antibody and the host are highly variable and difficult to predict⁶⁻⁸ and that the fact that an antibody is human or has been humanized does not necessarily translate to a safer, less immunogenic or more effective therapy. While the industry trend has been to favor development of human(ized) antibodies for much of the early 21st century, investigation into the relative benefits of human(ized) antibodies combined with enhanced understanding of disease

processes may support the re-emergence of murine-derived antibody therapies. Indeed, the recent European approval of the murine-derived tri-functional antibody catumaxomab supports this position.^{9,10}

Adverse Drug Reactions: Human(ized) Biologics and Immunogenicity

Highly specific and successful therapeutic mAbs have been developed for many disease conditions. Originally, mAbs were generated in mice against tumor antigens,¹¹ and their development provided unique tools to help combat malignancies, including lymphomas and leukemia.¹¹ During this time, development expanded to include those that could be utilized for immune modulation. The first antibody approved by the United States Food and Drug Administration, OKT3, was a highly mitogenic murine anti-CD3 antibody approved for treatment of organ transplant rejection. While immunomodulating murine mAbs such as OKT3 have exhibited excellent therapeutic efficacy, their therapeutic utilization was limited by the association with adverse events arising from immunogenic responses to the therapeutic agent.¹²⁻¹⁶

Immunogenicity usually refers to the ability of a biologic agent to trigger an anti-drug-antibody response; however, we also include CRS resulting from either acute phase reactions or related to the pharmacological activity of an antibody as a immunogenic event often observed in patients treated with mAbs.¹⁷⁻²¹

The precise mechanism(s) through which immunogenicity occurs are poorly defined, but it is clear that adverse events are associated with both the pharmacological activity of an antibody, as well as less specific responses.¹⁸ Foreign proteins such as murine-derived antibodies are, upon infusion, internalized by cells with antigen presentation capabilities. Subsequent immune responses result in T-cell-dependent anti-drug-antibody production.¹⁷⁻²¹ This process was thought to occur for all murine antibodies; however, subsequent analysis has shown that 20% of murine-derived therapeutic antibodies induce negligible/tolerable levels of HAMA.¹⁹

It was hoped that the generation of humanized and fully human antibodies would circumvent the induction of anti-drug antibodies altogether, but this has not been the case. For example, humanized mAbs anti-CD3 teplizumab^{14,16} and anti-CD52 alemtuzumab and human anti-tumor necrosis factor adalimumab, are all capable of triggering human anti-human antibodies (HAHA).⁷ Alemtuzumab has been shown to cause HAHA responses in 63% of rheumatoid arthritis patients and up to 23% of multiple sclerosis patients in Phase 1 and 2 studies, respectively.^{7,8,22} Adalimumab can have up to 89% HAHA incidence, even though it is a fully human antibody.^{4,7,8,13,14,16,17,23-30} The generation of anti-drug-antibodies is usually regarded as a negative outcome, with reductions in efficacy an obvious concern. However, in some instances the formation of high HAMA titers have correlated with increased therapeutic efficacy of certain antibodies.^{31,32} For instance, increased survival was observed in non-Hodgkin lymphoma patients administered Lym-1 who developed high levels of HAMA.³¹ The precise mechanism through which HAMA may mediate increased anti-cancer activity remains to be completely defined. However, the formation of idiotypic antibodies against the therapeutic antibody, which may also bind to the targeted epitope, may enhance antibody-mediated tumor destruction through mechanisms such as antibody-dependent cell cytotoxicity or complement-dependent cytotoxicity.^{5,32}

It may also be argued that the formation of anti-drug antibodies is acceptable if clinical objectives have been met, e.g., rabbit anti-thymocyte globulin and alemtuzumab, which are agents utilized in transplantation.^{33,34} Both are associated with significant anti-drug antibody responses,^{8,35} but, since both are used as short course immune induction agents, the short term anti-drug globulin response has not been described as a significant clinical concern.

One critical element of mAb therapy is the development of CRS,¹⁷ which is the result of excessive secretion of pro-inflammatory mediators. While in some cases CRS may play a critical role in mAb-based therapeutics, it is usually considered to be

Table 1. Human(ized) and rodent derived antibodies that have been tested in humans

Antibody INN (Trade name)	Antibody type (Generation Technique)	Target	Observed adverse events	Anti-drug antibodies	References
Antibodies targeting cytokines					
Adalimumab (<i>Humira</i>)	Human (phage display)	TNF	Infections, fever, diarrhea, rash	++++ Neutralizing	Bender, et al. 2007; ⁴⁸ Coenen, et al. 2007 ⁴⁹
Golimumab (<i>Simponi</i>)	Human (transgenic mouse)	TNF	Infusion reactions, nausea, infections	+ Non-neutralizing	Shealy, et al. 2010, ⁵⁰ Kay, et al. 2010, ⁵¹ Kay, et al. 2008 ⁵²
Certolizumab pegol (<i>Cimzia</i>)	Humanized Fab	TNF	Abdominal pain, diarrhea, injection site reactions, infection	+ Neutralizing	Baker 2009, ⁵³ Lichtenstein, et al. 2010 ⁵⁴
Briakinumab	Human (phage display)	IL12/IL23p40	Infections, fever, diarrhea, malignancies	Unknown	Gandhi, et al. 2010 ⁵⁵
Ustekinumab (<i>Stelara</i>)	Human (transgenic mouse)	IL12/IL23p40	Fatigue, headache, cardiac toxicity, infections	+ Neutralizing	Gandhi, et al. 2010, ⁵⁵ Cingoz 2009 ⁵⁶
Canakinumab (<i>Ilaris</i>)	Human (transgenic mouse)	IL1	Infections	None Described	Dhimolea 2010, ⁵⁷ Lachmann, et al. 2009 ⁵⁸
Tocilizumab/ Atlizumab (<i>Actemra</i>)	Humanized	IL6 receptor	Infusion reactions, infections, malignancy, anaphylaxis	+ Neutralizing	Sharma, et al. 2008 ⁵⁹
Lerdelimumab	Human (phage display)	TGFβ	Eye based infusion-Cataracts, pain, conjunctivitis	+ Non-neutralizing	Khaw, et al. 2007 ⁶⁰
B-E8	Murine	IL6	Headache, vomiting, fever, thrombocytopenia	+ Non-neutralizing	Rossi, et al. 2005, ⁶¹ Emilie, et al. 1994 ⁶²
CB6	Murine	TNF	Infections, headache, vomiting, fever, infusion reactions	+++++	Fisher, et al. 1993 ⁶³
B-N10	Murine	IL10	Infusion reactions	+++++ Neutralizing	Llorente, et al. 2000 ⁶⁴
Afelimomab	Murine Fab	TNF	Infections, headache, vomiting, fever, infusion reactions	++ Non-neutralizing	Panacek, et al. 2004, ⁶⁵ Reinhart, et al. 2001 ⁶⁶
Nerelimumab	Murine	TNF	Serum sickness, hypotension	+++++	Cohen and Carlet 1996 ⁶⁷
Antibodies targeting T cells					
Zanolimumab	Human (transgenic mouse)	CD4	Infusion reactions, infections, malignancies	+ Non-neutralizing	Mestel, et al. 2008 ⁶⁸
Ipilimumab	Human (transgenic mouse)	CTLA-4 (CD152)	Infusion reactions Anemia/diarrhea Autoimmune enterocolitis Antibody-induced lupus nephritis	None Described	Ansell, et al. 2009, ⁶⁹ Weber, et al. 2009, ⁷⁰ Weber 2009, ⁷¹ Sanderson, et al. 2005 ⁷²
Tremelimumab	Human (transgenic mouse)	CTLA-4 (CD152)	Fever, diarrhea, chills, endocrine disorders, anti-thyroid disorders	None Described	Kirkwood, et al. 2010, ⁷³ Camacho 2008 ⁷⁴
Alemtuzumab (<i>Campath 1H</i>)	Humanized	CD52	Infusion reactions, infections, malignancies	+++ Neutralizing	Waldmann and Hale 2005 ³
Teplizumab	Humanized	CD3	Cytokine release, fever, anemia, vomiting, nausea, arthralgia, headache	+++ Neutralizing	Herold, et al. 2002 ¹⁵
Vedolizumab	Humanized	Alpha4 Beta7 Integrin	92% of subjects experienced AEs (Grade 1), hypersensitivity	++ Neutralizing	Baumgart 2010, ⁷⁵ Soler, et al. 2009 ⁷⁶
Visilizumab	Humanized	CD3	Headache, cytokine release syndrome, fever, rigors, infections	+++ Non-neutralizing	Baumgart, et al. 2010 ⁷⁷

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Antibody INN (Trade name)	Antibody type (Generation Technique)	Target	Observed adverse events	Anti-drug antibodies	References
Antibodies targeting T cells (continued)					
Zolimomab aritox	Murine, conjugated to ricin toxin	CD5	Rash, liver toxicity, diarrhea, nausea/vomiting	+ Non-neutralizing	Martin, et al. 1996 ⁷⁸
Muromonab (Orthoclone)	Murine	CD3	Cytokine release syndrome, pulmonary edema, coagulation disorders	++++ Neutralizing	Sgro 1995 ⁷⁹
T10B9	Murine	αβTCR	Fever, chills	++	Waid, et al. 1997 ⁸⁰
BMA-031	Murine	αβTCR	Headache, joint pain, muscle stiffness diarrhea	+++ Neutralizing	Knight, et al. 1994 ⁸¹
Telimomab & Telimomab Aritox	Murine, conjugated with ricin toxin	T65 antigen	Urticaria, diarrhea, cough, hypotension	None Described	Dillman, et al. 1982, ⁸² Schroff, et al. 1984 ⁸³
33B.1	Murine	IL2 receptor	Chills, fever, diarrhea, renal dysfunction	+++++ Neutralizing	Souillou, et al. 1990 ⁸⁴
B-F5	Murine	CD4	Cytokine release syndrome, nausea, headache, diarrhea	+++	Rumbach, et al. 1994, ⁸⁵ Racodot, et al. 1993 ⁸⁶
BTI-322	Murine	CD2	Infusion related nausea, vomiting, diarrhea, hypertension, tachycardia	None Detected	Przepiorka, et al. 1998 ⁸⁷
Antibodies targeting B cells/Antibody isotypes					
Ofatumumab (Arzerra)	Human (transgenic mouse)	CD20	Infections (occurred in 70%), infusion reactions, bronchospasm	None Described	Lemery, et al. 2010, ⁸⁸ Wierda, et al. 2010 ⁸⁹
Belimumab (Benlysta)	Human (phage display)	BlyS	Moderate infusion reactions: headache, rash	+ Neutralizing	Ding 2008, ⁹⁰ Furie, et al. 2009 ⁹¹
Omalizumab (Xolair)	Humanized	IgE	Anaphylaxis, malignancies, infections, injection site reactions	+ Non-neutralizing	Rodrigo, et al. 2010, ⁹² Easthope and Jarvis 2001 ⁹³
Ocrelizumab	Humanized	CD20	Infections, malignancies	Inversely related to dose, lower doses= +++ Neutralizing	Genovese, et al. 2008 ⁹⁴
Epratuzumab- ⁹⁰ Y	Humanized, radiolabeled	CD22	Fever, rash, diarrhea, infusion reactions	None Described	Leonard, et al. 2005, ⁹⁵ Leonard, et al. 2004, ⁹⁶ Morschhauser, et al. 2010 ⁹⁷
RFB4-Ricin A	Murine, conjugated to ricin A toxin	CD22	Pulmonary edema, tachycardia, fever, infection, vascular leak syndrome	++	Vitetta, et al. 1991 ⁹⁸
Ibritumomab tiuxetan (Zevalin)	Murine, conjugated to tiuxetan	CD20	Fatigue, nausea, chills, diarrhea, thrombocytopenia, neutropenia	++	Wang, et al. 2009 ⁹⁹
Tositumomab- ¹³¹ I (Bexxar)	Murine, radiolabeled	CD20	Infusion reactions, hypotension, rigors, fever, wheezing, edema, arthralgia & infections.	+ Neutralizing	Kaminski, et al. 2001 ¹⁰⁰
General immune targets (not developed initially to target T cell, B cell or cancer targets)					
Eculizumab (Soliris)	Humanized	Complement C5	Infections, fever, nausea, diarrhea	+ Non-neutralizing	Dubois and Cohen 2009 ¹⁰¹

Table 1. Human(ized) and rodent derived antibodies that have been tested in humans

Antibody INN (Trade name)	Antibody type (Generation Technique)	Target	Observed adverse events	Anti-drug antibodies	References
General immune targets (not developed initially to target T cell, B cell or cancer targets) (continued)					
Natalizumab (<i>Tysabri</i>)	Humanized	Alpha4 Beta1 & Alpha4 Beta7	Infusion reactions, headache, fever, malignancy, infection (PML)	+	Selewski, et al. 2010, ¹⁰² Johnson 2007, ¹⁰³ Stuve and Bennett 2007 ¹⁰⁴
Efalizumab (<i>Raptiva</i>)	Humanized	CD11a	Infections: sepsis, viral meningitis, PML	++	Vincenti, et al. 2007 ¹⁰⁵
Rovelizumab	Humanized	CD18	Infusion reactions (30%); Infections common	Unknown	Rusnak, et al. 2001 ¹⁰⁶
Denosumab (<i>Prolia</i>)	Human (transgenic mouse)	RANKL	Infections, arthralgia, infusion reactions	++ Non-neutralizing	Ellis, et al. 2008 ¹⁰⁷
Abciximab (<i>ReoPro</i>)	Chimeric	GPIIb/IIIa	Bleeding disorders	++	Brener, et al. 2003 ¹⁰⁸
LM-CD45 (YTH 54.12 & YTH 24.5)	Murine	CD45	Fever, chills, bronchospasm, urticaria, infections	Unknown	Brenner, et al. 2003, ¹⁰⁹ Krance, et al. 2003 ¹¹⁰
MDX-11, PM81	Murine	CD15	Fever, chills, Hypotension	+ Non-neutralizing	Ball, et al. 1995 ¹¹¹
HRS-3/9	Murine, bispecific	CD30, CD16	Fever, allergic exanthema, hypotension	+++ Anaphylaxis-inducing	Hartmann, et al. 1997 ¹¹²
Enlimomab	Murine	CD54 (ICAM)	Headache, fever, pneumonia, sepsis, cardiac failure	+++++ Neutralizing	Schneider, et al. 1998 ¹¹³
Vepalimomab	Murine	VAP-1	Headache, fever, eczema	++ Neutralizing	Vainio, et al. 2005 ¹¹⁴
Odulimomab	Murine	CD11a	Infection, thrombocytopenia, neutropenia	+++	Hourmant, et al. 1996 ¹¹⁵
ETI-104	Murine, conjugated to double stranded DNA	Human Complement Receptor 1	Infusion reactions, headache	+++++	Iking-Konert, et al. 2004 ¹¹⁶
Antibodies targeting cancer-associated antigens					
Panitumumab	Human (transgenic mouse)	EGF receptor	Infusion reactions, pulmonary fibrosis, dermatological toxicity with infectious sequelae	None described	Van Cutsem, et al. 2008, ¹¹⁷ Van Cutsem, et al. 2007, ¹¹⁸ Cohenuram and Saif 2007 ¹¹⁹
Zalutumumab	Human (transgenic mouse)	EGF receptor	Infusion reactions, electrolyte imbalances, infections, rash	Unknown	Rivera, et al. 2009 ¹²⁰
Ramucirumab	Human (phage display)	VEGF receptor-2	Dose limiting AE induction, hypertension, liver toxicity, gastrointestinal AE	None described	Spratlin, et al. 2010 ¹²¹
Bevacizumab (<i>Avastin</i>)	Humanized	VEGF	Infusion reactions, hypersensitivity reactions, gastrointestinal perforation, wound healing concerns	None described	Lubner, et al. 2010 ¹²²
Necitumumab	Human (phage display)	EGF receptor	Rash, grade 3 skin reactions	Unknown	Kuonen, et al. 2010 ¹²³

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Antibody INN (Trade name)	Antibody type (Generation Technique)	Target	Observed adverse events	Anti-drug antibodies	References
Antibodies targeting cancer-associated antigens (continued)					
Trastuzumab (<i>Herceptin</i>)	Humanized	HER-2	Heart attack, infusion reactions, infections	+ Non-neutralizing	Package insert ¹²⁴
Pertuzumab	Humanized	HER-2	Infusion reactions (in 50% of patients, grade 3–4), hemolytic uremic syndrome	None Described	Agus, et al. 2005 ¹²⁵
Farletuzumab	Humanized	Folate Receptor	AEs occurred in 80% of patients: infusion reactions, hypersensitivity, nausea	Unknown	Ebel, et al. 2007, ¹²⁶ Spannuth, et al. 2010 ¹²⁷
Figitumumab	Human (transgenic mouse)	IGF-1R	Fever, hyperglycemia, nausea, diarrhea	None Described	Olmos, et al. 2010, ¹²⁸ Karp, et al. 2009 ¹²⁹
L-6	Chimeric	Tumor Associated Antigen L6	Fever, nausea, chills	++	O'Donnell, et al. 1998 ¹³⁰
Anti-CEA-radiolabeled	Chimeric	Carcino-embryonic Antigen	Hematological toxicity	++ Neutralizing	Buchegger, et al. 1995, ¹³¹ Behr, et al. 1997 ¹³²
Anti-CEA-radiolabeled (Iodine 131)	Murine	Carcino-embryonic Antigen	Hematological toxicity	+++++ Neutralizing	Buchegger, et al. 1995 ¹³¹
Anti-CEA-radiolabeled (Rhenium 188)	Murine	Carcino-embryonic Antigen	None described	+	Juweid, et al. 1998 ¹³³
EMD 559000	Murine	Epidermal Growth Factor Receptor	Injection reactions	+++++ Non-neutralizing	Faillot, et al. 1996 ¹³⁴
Capromab	Murine	Prostate Specific Membrane Antigen	Infusion reactions, Grade 2 leukopenia	+	Deb, et al. 1996 ¹³⁵
XMME-001-RTA	Murine	Melanoma antigens	Profound fatigue, myalgia, arthralgia, edema.	++++	Gonzalez, et al. 1991, ¹³⁶ Spitler, et al. 1987 ¹³⁷
KS1/4 MTX-Mab, conjugated	Murine	EpCam	Fever, anorexia, nausea, vomiting, diarrhea, abdominal pain, acute immune complex mediated reaction	++++	Elias, et al. 1994, ¹³⁸ Elias, et al. 1990 ¹³⁹
Nofetumomab streptavidin	Murine, conjugated to streptavidin	EpCam	Diarrhea, nausea, vomiting, hematological toxicity	++++ Neutralizing	Knox, et al. 2000 ¹⁴⁰
BIWA1	Murine	CD44v6	Fever, Infusion reaction	+++++ Transient	Stroomeer, et al. 2000 ¹⁴¹
MDX-210	Murine, bispecific	Her-2, CD64	Fever, malaise, hypertension	++++ Neutralizing Transient	Valone, et al. 1995 ¹⁴²
OC/TR	Murine, bispecific	Ovarian Carcinoma Antigen, CD3	Infusion reactions, cytokine release	++++ Increased HAMA (associated with increased efficacy)	Miotti, et al. 1999 ³²
Ertumaxomab	Murine, bispecific	Her-2/neu (Mouse), CD3 (Rat)	Infusion reactions, headache, vomiting, rigor, fever, liver toxicity	++	Jager, et al. 2009, ¹⁴³ Kiewe, et al. 2006 ¹⁴⁴
Catumaxomab (<i>Removab</i>)	Murine, bispecific	EpCam, (Mouse) CD3 (Rat)	Infusion reactions, headache, vomiting, rigor, fever, liver toxicity	+++++	Chelius, et al. 2010, ⁹ Sebastian, et al. 2009, ¹⁴⁵ Seimetz, et al. 2010 ¹⁰

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Antibody INN (Trade name)	Antibody type (Generation Technique)	Target	Observed adverse events	Anti-drug antibodies	References
Antibodies targeting cancer-associated antigens (continued)					
Naptumomab estafenatox	Murine Fab, conjugated to Staph. Enterotoxin A	Oncofetal Trophoblast Glycoprotein Antigen 5T Superantigen SAE/E120	Cytokine release, fever, nausea, diarrhea, chills and hypotension	+++	Borghaei, et al. 2009 ¹⁴⁶
Metuximab-I ¹³¹ (Licartin)	Murine Fab radiolabeled	Hepato-cellular Carcinoma Antigen HaB18G/CD147	Fever, nausea, vomiting, anorexia, stomach ache, diarrhea, infection	+	Chen, et al. 2006 ¹⁴⁷
Gavilimomab	Murine	CD147	Liver failure, myalgia, fever, hypotension	+	Deeg, et al. 2001 ¹⁴⁸
Pemtumomab- ⁹⁰ Y	Murine, radiolabeled	Mucin 1	Nausea, fatigue, arthralgia, myalgia, abdominal pain, rash, diarrhea, vomiting	+++++ HAMA (associated with increased efficacy)	Oei, et al. 2008, ¹⁴⁹ Verheijen, et al. 2006 ¹⁵⁰
Anatumomab mafenatox	Murine Fab, conjugated to Staph. Enterotoxin A	5T4 Oncofetal Antigen	Fever, hypotension, nausea, vomiting	++++	Shaw, et al. 2007 ¹⁵¹
Lym-1	Murine	HLA-DR10	Fever, nausea, vomiting, pruritus, urticaria, bronchospasm	++ HAMA associated with increased efficacy	Azinovic, et al. 2006, ³¹ DeNardo, et al. 2003, ⁵ Kuzel, et al. 1993 ¹⁵²
Antibodies targeting infectious antigens					
Nebacumab (Centoxin)	Human	Endotoxin	Hypotension, anaphylaxis	Unknown	Derkx, et al. 1999 ¹⁵³
T88	Human (Trioma-based fusion technology)	Lipo-polysaccharide	Hypotension, anaphylaxis	Unknown	Daifuku, et al. 1992, ¹⁵⁴ Albertson, et al. 2003 ¹⁵⁵
Raxibacumab	Human (phage display)	<i>B. anthracis</i> PA	Infections, headache	Unknown	Migone, et al. 2009 ¹⁵⁶
Edobacomab	Murine	Core Lipid A Region of Bacterial Endotoxin	Limited toxicity described	+++	Harkonen, et al. 1988 ¹⁵⁷

General clinical responses have been described based on the available literature. The ability to induce anti-drug-antibodies is described as a percentage of patients treated, using the following scale, 0–20 (+); 21–40 (++); 41–60 (+++); 61–80 (++++); 81–100 (+++++). In addition, where applicable, the ability of these antibodies to neutralize the monoclonal in question is also described. AE, adverse events; BlyS, B lymphocyte stimulator; CD, cluster of differentiation; CTLA, cytotoxic T lymphocyte antigen 4; EGF, epidermal growth factor; EpCAM, epithelial cell adhesion molecule; GP, glycoprotein; HER, human epidermal growth factor receptor; HLA-DR, human leukocyte antigen DR; ICAM, intracellular adhesion molecule; Ig, Immunoglobulin; IGF-1R, insulin-like growth factor-1 receptor; IL, interleukin; PA, protective antigen; PML, progressive multifocal leukoencephalopathy; RANKL, receptor activator of nuclear factor kappaB ligand; TCR, T-cell receptor; TGF, transforming growth factor; TNF, tumor necrosis factor; VAP, vascular adhesion protein; VEGF, vascular endothelial growth factor; Y, yttrium.

a significant safety concern. Sensitization to murine components of antibodies has been described as a major cause for CRS; however, CRS is rarely caused by IgE-mediated anaphylaxis. Usually CRS is mild and self-limiting, with acute phase responses, also referred to as first dose reactions, thought to result from antibody-Fc

receptor interactions.^{17,23} However, CRS can be the result of pharmacological interactions, such as those observed in patients treated with TGN1412 and can be life-threatening.^{24–26} Another example includes the cross-linking ability of OKT3, which may culminate in substantial T-cell activation and cytokine

release.¹⁶ This response was originally thought to be mostly due to Fc binding and subsequent antigen presentation of OKT3 to T cells, but humanization and the reduction of Fc interactions have led to only modest increases in the safety of anti-CD3 antibodies.^{13,14,27} Alemtuzumab may also trigger significant CRS, even at low

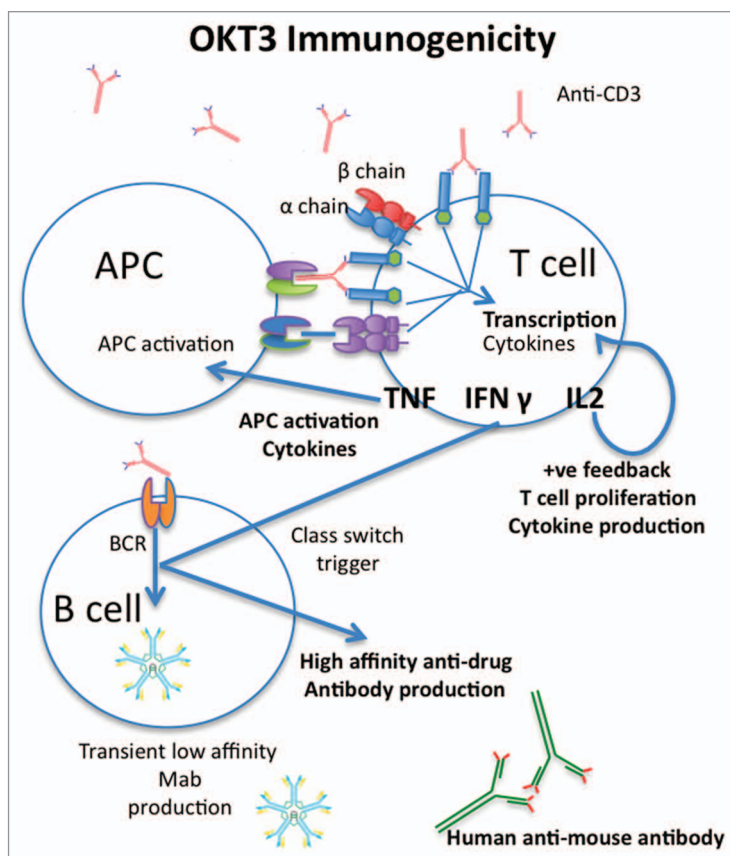


Figure 1. Immunogenicity of monoclonal antibodies. There are numerous mechanisms that may account for the immunogenicity of monoclonal antibodies. Importantly, many of these phenomena act synergistically, potentiating life-threatening immune responses. In the case of anti-CD3 antibodies such as OKT3, the antibody can bind to the CD3 receptor freely, or in the context of antigen-presenting cells (APCs) through Fc receptor binding. This presentation cross-links the CD3 molecule on the T-cell surface, triggering immunoreceptor tyrosine-based activation motif (ITAM)-mediated T-cell activation. In the case of some human antibodies, complementarity-determining regions may also be presented to the T cells in the context of major histocompatibility complex. No matter the form of T-cell presentation, all trigger ITAM-mediated cytokine production. Some cytokines, including interleukin (IL)-2, act in a positive feedback loop on the T cells, causing further T-cell activation, proliferation and cytokine production. Other cytokines, such as tumor necrosis factor (TNF), mediate febrile responses and, in conjunction with interferon (IFN) γ , activate APCs, which may produce their own set of pro-inflammatory cytokines. In addition to APC activation, IFN γ also stimulates affinity maturation in B cells, also known as class switching. Initially, B cells will produce transient low-affinity antibodies, with little to no clinical relevance. However, cytokines such as IFN γ drive B cells to produce antibodies with high affinity. In the context of protein therapeutics, these antibodies are usually IgG antibodies that may exhibit long serum half lives and neutralizing properties.

doses.⁷ CRS in this case has been argued to be associated with alemtuzumab's interaction with its CD52 ligand and its triggering of danger signals associated with cellular depletion and target cell lysis.²⁸ Finally, T-cell epitopes embedded within antibody CDRs, such as those described for golimumab, are also capable of stimulating cytokine release through their T-cell stimulating potential.⁴

Anti-drug-antibody responses and CRS may appear as separate issues, but

CRS may actually potentiate the anti-globulin response, with cytokine being released through target cross-linking (as observed with OKT3; Fig. 1) and possibly danger signals resulting from cellular lysis (as observed for alemtuzumab). Furthermore, IFN γ produced by CD4 T cells activated by CDR epitopes found on some fully human antibodies may also support B-cell production of human anti-human antibodies (HAHA).⁴ The ability of CRS to support anti-drug globulin

responses has been described clinically in renal transplant patients undergoing renal transplantation, whereby chemical immune suppression, with cyclosporine significantly reduces HAMA induction observed in OKT3 treated patients.³⁶

The clinical relevance of immunogenicity is far-reaching and highly antibody dependent. Cytokine release is a serious event that can cause death, while the formation of anti-drug antibodies may have much milder consequences. For mAbs, anti-drug globulin responses seem in most cases to be either mild or, at minimum, short-lived.^{29,30} Indeed, the generation of anti-alemtuzumab antibodies in multiple sclerosis (MS) patients have been mostly described as short-lived and not preclusive to re-dosing; however, the anti-drug antibodies have also been found to reduce the efficacy of alemtuzumab in some patients.⁸ In addition, HAMA development in adalimumab-treated patients may be neutralizing in up to 89% of patients.⁴

These examples suggest that the immunogenicity of certain mAbs is not simply explained by the process through which it was derived, with both animal-derived and fully human therapeutic antibodies capable of eliciting anti-drug and cytokine responses. The overall impact of immunogenicity will be ultimately determined by clinical goals and the response observed in treated patients; the immunogenicity data will aid in the assessment of safety versus the overall benefits of disease reduction associated with biologics.

Monoclonal Antibody Therapy in Oncology

Murine antibody humanization may enhance the serum half-life of mAbs, a feature that is often considered to be an important element for enhancing therapeutic efficacy. For example, such an effect was observed upon humanization of the rat antibody CAMPATH-1G, which yielded alemtuzumab (Campath-1H). Alemtuzumab was first approved for chronic lymphocytic leukemia in 2001.³ Comparisons of alemtuzumab to its rat predecessor showed that the humanized form of this antibody exhibited a longer

half-life and enhanced therapeutic effect in lymphocytic leukemia patients.³ The increase in half-life, however, has also been suggested to play a significant role in the high levels of infection, malignancies and autoimmune disease development observed in alemtuzumab-treated patients.^{3,6,22,37,38} While these risks become less of a concern in cases of terminal cancer, they may pose a significant issue during treatment of patients requiring longer-term administration, including those with early stage cancers or chronic disorders such as type 1 diabetes (T1D), MS and other autoimmune diseases.

The recent approval of the rat/mouse hybrid tri-functional antibody, catumaxomab, suggests that the ability of mAbs to destroy malignant cells is of significant importance. In this case, the product was approved in the European Union due to the overall benefit of catumaxomab to patients suffering malignant ascites, even though it is associated with numerous adverse events, including anti-drug antibody development and CRS.¹⁰ The induction of CRS may play a significant role in the therapeutic utility of catumaxomab. The induction of pro-inflammatory cytokines has been suggested to play an important role in switching cytokine profiles from those that may favor tumor development to one that drives immune-mediated tumor destruction, suggesting that CRS may be an important event in the efficacy of future anti-cancer monoclonal antibody therapies.

In addition, the precise reasons for the observation of the enhanced effectiveness of murine Lym-1 in patients who developed HAMA^{31,30} remain to be defined, but the results highlight the need for further research into the properties of HAMA besides the well-known ability of these antibodies to neutralize therapeutic agents. The data suggest that the generation of anti-drug antibodies should not preclude the testing of such agents in certain disease conditions.

Monoclonal Antibody Therapy in T-Cell-Mediated Autoimmune Disease

Scientific and clinical evidence supporting the use of mAb therapies in autoimmune

diseases such as T1D and MS is mounting.^{13-15,27,39,40} Data suggest that therapies that specifically target activated pathogenic T cells while leaving other elements of the immune system unaltered are likely to have the greatest success in treating T-cell-mediated autoimmune disease. T1D and MS are considered to be chronic diseases in which the severity of symptoms increases over time and currently available therapies fail to effectively inhibit disease progression in the majority of patients. As a result, patients will eventually succumb to the disease. Studies of the pathogenesis of T1D and MS clinically and in animal models have uncovered a unique phenomenon, known as epitope spreading,^{41,42} in which a cascade of responses to different auto-antigens arise over the course of the disease.^{43,44} Experimental and clinical data have shown that early intervention in this cascade (before irreparable damage to the targeted organ has occurred) can have dramatic and long-term positive effects.

In animal models, short course immune induction therapy (SCIIT) with mAbs against murine $\alpha\beta$ T-cell receptor (TCR) or CD3 is capable of preventing diabetes development^{40,45} and is effective therapy in the experimental autoimmune encephalomyelitis model of MS.⁴⁶ Importantly, these findings have recently been translated to human clinical disease. Clinical trials using SCIIT in T1D patients have also shown promise,^{13,14,27} with humanized anti-CD3 resulting in reduced insulin requirements, in some cases lasting many years. Unfortunately, the humanized anti-CD3 therapies tested were still associated with anti-drug antibody development, CRS or reactivation of Epstein-Barr virus.^{13,14,27} These data validate development of mAbs that target T cells as methods for modifying these autoimmune diseases, but support the need to generate therapeutics with less severe adverse events. Humanization of CD3 antibodies has not necessarily provided this increase in safety, suggesting that increased understanding of host-biologic interactions is required. With this in mind, it is possible that other T-cell targets will provide similar therapeutic outcomes without the same adverse events. Other T-cell antibodies in clinical development, such as alefacept (anti-CD2)⁴⁷ or TOL101

(anti- $\alpha\beta$ TCR antibody), may provide this T-cell targeting profile. Preliminary data with alefacept suggest that targeting CD2 may only offer moderate T-cell manipulation and questions remain regarding safety concerns, which will require further analysis.⁴⁷ Further work is required to validate using anti- $\alpha\beta$ TCR to target T cells. Unlike the CD3 proteins, the $\alpha\beta$ TCR antibody lacks intracellular immunoreceptor tyrosine-based activation motifs (ITAMS), which are in part responsible for the mitogenic effects of anti-CD3 antibodies. As such, targeting the $\alpha\beta$ TCR may provide a unique method for inactivating T cells.

Conclusion

Many factors should be taken into consideration when making the decision to humanize a murine mAb. The inherent immunogenicity of the murine protein plays a critical role, but, as evidenced by studies of humanized anti-CD3 antibodies and a number of fully human antibodies, engineering of human/humanized antibodies is not guaranteed to completely reduce or prevent immunogenic issues including anti-drug antibody development. The therapeutic target may also need to be considered, for example, targeting the major TCR signaling protein CD3 results in mitogenic effects, which is not surprising. The indication also plays a substantial role in the decision of whether or not to humanize an antibody. In an indication such as cancer, in which long half-lives have been shown to play a beneficial role in tumor clearance, humanization can have benefits. Alemtuzumab has demonstrated the favorable effects of long half-life in cancer indications. In contrast, in indications in which short course immune induction therapy has been shown to be significantly advantageous, e.g., T1D or MS, the rapid clearance of non-human antibodies may prove to be a beneficial feature.

Another complicated factor in mAb development may reside in the contribution of cytokine release and anti-drug-antibody development. It appears, at least in some cancer indications, that both of these factors may play significant roles in increasing the efficacy of certain biologics.

In conclusion, the utility of humanized antibodies hinges on the immunogenicity of the original antibody in combination with the characteristics of the targeted therapeutic indication. Moving immediately to testing fully human antibodies may not only fail to provide the safety and efficacy desired, but may also result in discounting future testing of targets that hold significant therapeutic promise. In some cases, a humanized murine antibody may provide a unique therapeutic advantage in one disease setting, while its murine predecessor may show increased efficacy in others. Important steps in the future will be to identify and design predictive models that may aid in the resolution of appropriate forms of certain biologics for therapeutic use.

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